ORIGINAL ARTICLE

Serum Liver and Pancreatic Enzymes in Chronic Kidney Disease with and without End-stage Renal Disease: A Comparative Study

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Abstract

Introduction: Chronic kidney disease (CKD) is emerging as an important chronic disease globally. The occurrence of liver and pancreatic diseases as comorbid conditions is very common. Estimation of liver and pancreatic enzymes still remains the main modality of diagnosis and monitoring hepatic and pancreatic diseases. Alterations in the enzyme levels in the absence of liver and pancreatic diseases have been reported. Hence we decided to compare the serum levels of liver and pancreatic enzymes (AST, ALT, ALP, GGT amylase and lipase) among CKD patients without end-stage renal disease (ESRD), patients with ESRD and healthy controls and to correlate the enzyme levels with eGFR (severity).

Materials and methods: The present study was conducted in a tertiary care hospital with 100 controls, 100 CKD patients without ESRD and 100 ESRD patients. All the 300 patients had no evidence of hepatic or pancreatic diseases. Alanine transaminase (AST), aspartate transaminase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), amylase and lipase were estimated in all 300 study subjects.

Results: There was a significant decrease in the levels of AST and ALT and increase in ALP, GGT, amylase and lipase levels in the CKD patients without ESRD and ESRD patients as compared to the controls ($p < 0.05$). eGFR was found to have a strong negative correlation with ALP, amylase, and lipase in CKD patients without ESRD and with ESRD.

Conclusion: Our study emphasizes that, using the present reference ranges for these enzymes in CKD patients will result misdiagnosis of hepatic or pancreatic disease, hence emphasizing the need to establish new reference ranges for these enzymes in various stages of CKD which ultimately will help the treating physicians in diagnosis and management of hepatic and pancreatic dysfunction in CKD patients.

Keywords: Chronic kidney disease, GFR, Hepatic and pancreatic enzymes.

Indian Journal of Medical Biochemistry (2019): 10.5005/jp-journals-10054-0087

Introduction

Chronic kidney disease (CKD) is a worldwide public health problem which affects about 5–10% of the world population and 7% of the Indian population.[1] The highest reported prevalence of CKD by an Indian study was 6.3% for stage 3 CKD.[2,3] As the prevalence of diabetes and hypertension is alarmingly rising, the prevalence of CKD is expected to rise, and obviously this is the key target population on which this research can be conducted the kidney disease outcomes quality initiative (KDOQI) of the National Kidney Foundation (NKF) defines chronic kidney disease as either kidney damage for more than three months or a glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2 for three or more months with or without kidney damage.[4] KDOQI classified chronic kidney disease into five stages based on GFR and a GFR less than 15 mL/min/1.73m^2 is called stage 5 or ESRD.[5] Stage 1 or 2 CKD patients' progress to more advanced stages at approximately 0.5% per year.[6]

Liver and pancreatic diseases are common among chronic kidney disease patients. The most important chronic liver diseases associated with the chronic renal disease are hepatitis B and C[7] followed by alcoholic liver disease and non-alcoholic fatty liver disease (NAFLD) and liver cirrhosis due to many reasons like autoimmune hepatitis, and hemochromatosis. Hepatitis B and C infections can occur in ESRD patients due to hemodialysis. The other liver diseases can occur as comorbid conditions in CKD. Recent evidence suggests that nonalcoholic fatty liver disease is associated with an increased prevalence and incidence of chronic renal disease. The prevalence of HCV positive among hemodialysis patients can vary from < 5% to as high as 60% from different regions in the world.[8,9] Serum liver enzymes play an important role in diagnosing and monitoring these patients. Liver enzymes namely ALT, AST, ALP and GGT are elevated in several diseases, such as chronic viral hepatitis, nonalcoholic fatty liver disease, autoimmune hepatitis and alcoholic liver disease, which may exist as comorbid conditions in CKD.

Serum amylase and lipase are the pancreatic enzymes used for the assessment and monitoring many pathological states of pancreas like alcohol-induced pancreatitis and stones in the gall bladder or common bile duct, whose frequency of occurrence is high in CKD.[10] Amylase is one enzyme that is rapidly excreted by kidney, thus patients in chronic kidney disease have elevated serum pancreatic enzymes. Few studies have revealed alterations in these enzyme levels like elevated amylase and decreased transaminases in CKD even in the absence of hepatic or pancreatic diseases leading to misdiagnosis.[11,12] Many studies have reported elevated ALP levels in ESRD even in the absence of any coexisting hepatobiliary diseases. Elevated ALP is associated with increased risk of coronary artery calcification and mortality. Assumptions are that the rise in ALP may

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How to cite this article: Manju M, Rajendran S, Mishra S, Pavithra M. Serum Liver and Pancreatic Enzymes in Chronic Kidney Disease with and without End-stage Renal Disease: A Comparative Study. Indian J Med Biochem 2019;23(1):207-212.

Source of support: Nil

Conflict of interest: None

be due to the development of osteodystrophy (high turn over bone disease) as a complication of CKD. Since the diagnosis, assessment, monitoring and follow up of many hepatic and pancreatic diseases is based upon the levels of these enzymes, the accurate clinical assessment of the patient with ESRD is hampered by a paucity of knowledge concerning the serum concentrations of these enzymes in various stages of CKD. There are not many studies from India about the hepatic and pancreatic enzyme levels in various stages of CKD. There are very few studies that have correlated the hepatic and pancreatic enzyme levels with the severity of CKD. With this background, we decided to conduct this study to compare the hepatic and pancreatic enzyme (AST, ALT, ALP, GGT, amylase, and lipase) levels between CKD patients with ESRD and without ESRD and correlate these levels with the severity (estimated GFR or eGFR) of CKD.

Materials and Methods

Sample Size and Design

It was a hospital-based observational (case-control) study, which was carried out in Aarupadai Veedu Medical College. The subjects for the study were recruited from the Department of Nephrology (both outpatients and inpatients) by random sampling method. Age and sex-matched 300 subjects were divided into three groups - Control group included 100 apparently healthy subjects (eGFR > 60 mL/minute/1.73m^2), Second group included 100 CKD patients with no ESRD (eGFR between 15 and 60 mL/minute/1.73m^2) and the third group included 100 CKD patients with ESRD (eGFR < 15 mL/min/1.73m^2) or stage 5 CKD. ESRD and no ESRD CKD patients were diagnosed on the basis of KDOQI criteria. The study was started after getting the approval from the scientific research Committee and ethical committee of the institute. Informed consent was obtained from all the subjects included in the study, after explaining the procedure and aims of the study. Age, sex and detailed medical history about the subjects were collected using a pre-tested, semi-structured questionnaire.

Inclusion Criteria

Subjects of age more than 30 years of both sexes who satisfy KDOQI criteria.

Exclusion Criteria

Subjects with a history or evidence of any liver disease, HbsAg /HCV positive, pancreatitis and intake of drugs which affect liver enzymes like antiepileptic medicines, statins, INH, etc. and drugs that affect pancreatic enzymes like sitagliptin, etc.

Sample Collection

Five mL of venous blood sample was taken from all the subjects included in the study. The parameters that were measured were serum urea, creatinine, ALT, AST, ALP, GGT, amylase, and lipase and were assayed in the fully automated biochemistry analyzer (Mindray, BS 380). Samples were tested only after three levels of internal QC passed the quality checks. Urea was estimated by urease GLDH UV method, creatinine by modified Jaffe's kinetic method, AST and ALT by IFCC UV method without PLP activation, ALP by IFCC modified method, GGT by Szasz IFCC method, amylase by kinetic colorimetric method using Ethylidene-G_7-PNP as substrate and lipase by kinetic colorimetric method using 1,2-o-dilauryl-rac-glycerol-3-glutaric acid-(6′-methylresorufin) ester (DGGR) as chromogenic substrate.

Estimated GFR (eGFR) was calculated using MDRD (Modification of Diet in Renal Disease study) equation:

$$eGFR = 186.3 \times (\text{plasma creatinine})^{-1.154} \times \text{age}^{-0.203}$$
$$(\times 0.742 \text{ for women})$$

Statistical Analysis

All the results were subjected to statistical analysis using SPSS 16 software (IBM Corporation, NY, USA). Without making any assumption about the distribution of data, normality distribution testing of the continuous variables was performed using the non-parametric test; Kolmogorov–Smirnov test (KS-test). Data were first analyzed and was found to be of normal distribution and hence the results were presented as mean ± SD. Comparison of means of various parameters among the three groups was done by one-way analysis of variance (ANOVA) test followed by the post-hoc analysis. A p value < 0.05 was considered as statistically significant. Correlation analysis was done by Pearsons and Spearman's rank correlation test to describe the relationship between the eGFR and liver and pancreatic enzymes. Receiver operating characteristic (ROC) curve analysis was done for finding the predictive cut-off value of eGFR below which the hepatic and pancreatic enzymes derangements can be expected.

Results

The present study included 300 subjects who were divided into three groups based on eGFR–100 controls, 100 CKD patients without ESRD and 100 ESRD patients. Table 1 shows the comparison of various parameters in these three study groups. There was no statistically significant difference ($p > 0.05$) among the mean ages of the three groups. There was a statistically significant decrease in the levels of aspartate transaminase (AST) and alanine transaminases (ALT) in the CKD patients without ESRD and in ESRD patients as

Table 1: Comparison of parameters among controls, CKD patients without ESRD and ESRD patients

Parameter	*Controls*	*CKD without ESRD*	*ESRD*
Urea	24.53 + 20.38	80.11 + 26.18	102.43 + 30.14
Creatinine	0.709 + 0.34	2.78 + 1.898	9.74 + 3.48
eGFR	144.57 + 60.17	33.35 + 12.59	7.11 + 3.2
AST	34.58 + 18.53	29.69 + 14.28*	27.58 + 13.16*
ALT	32.64 + 16.19	28.31 + 13.93*	25.2. + 13.2*
ALP	107.4 + 69.04	134 + 52.63*	182.52 + 83.79*†
GGT	42.77 + 35.17	69.14 + 57.6*	73.03 + 100.3*
Amylase	67.42 + 16.79	91.83+ 28.1*	100.7 + 42.82*†
Lipase	26.55 + 6.38	57.36 + 20*	64.08 + 15.03*†

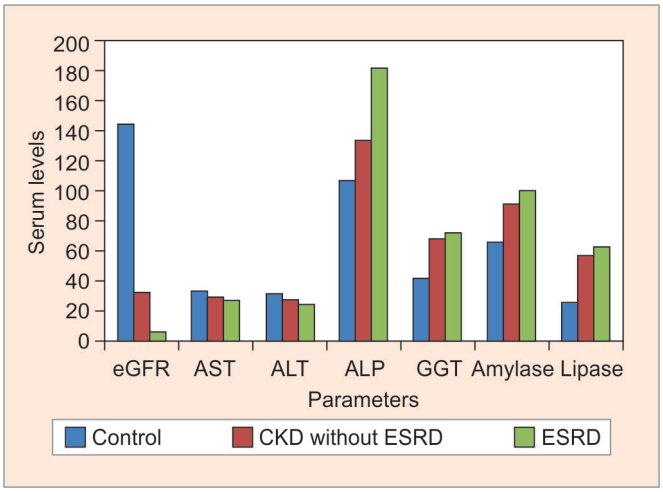
*$p < 0.05$ as compared to control; †p < 0.05as compared to CKD without ESRD.

compared to the controls ($p < 0.05$). Serum alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), amylase and lipase were significantly increased in the CKD patients without ESRD and in ESRD patients as compared to the controls ($p < 0.05$) (Graph 1). Serum levels of ALP, amylase, and lipase were significantly increased in the ESRD group as compared to CKD patients without ESRD. There was no statistically significant change in AST, ALT, and GGT between CKD without ESRD and ESRD patients.

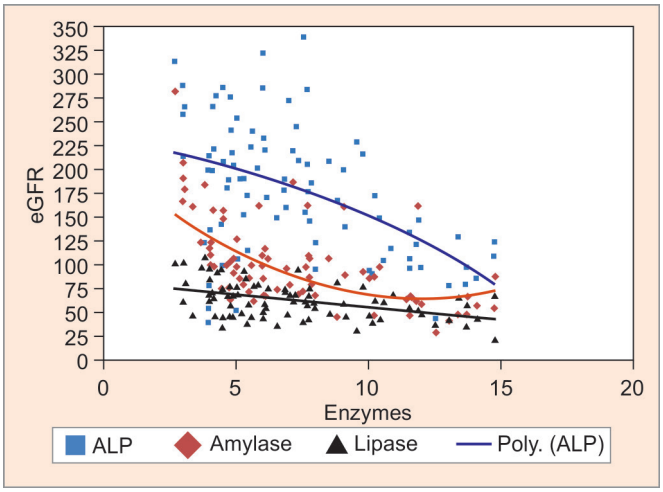
Table 2 shows the correlation analysis of eGFR with liver and pancreatic enzymes in controls and all CKD patients taken as a single group without diving into subgroups. Scatter diagram was plotted using eGFR on the Y-axis and ALP, amylase and lipase on the X-axis which is shown in Graph 2. Estimated glomerular filtration rate (eGFR) was found to have a strong negative correlation with ALP \(r = −0.54 p = 0.001), amylase (r = −0.41 p = 0.001) and lipase (r = −0.42 p = 0.001) in CKD patients without ESRD group. Similar strong negative correlation with ALP (r = −0.42 p = 0.001), amylase (r = −0.65 p = 0.001) and lipase (r = −0.46 p = 0.001) was found in ESRD patients also. There was no significant correlation between eGFR and any of these enzymes in the control group (Table 3). ROC curve analysis was performed and predictive cut off values found out for eGFR below which the derangements (increase) in levels of amylase, lipase, and ALP can be expected as shown in Table 4 and Graphs 3 to 5. The cut off value of eGFR was found to be 40, 48 and 47 mL/min for amylase lipase and ALP with a sensitivity of 90, 94 and 96% and specificity of 79, 86 and 80% respectively. AUC was 0.595 + 0.049 ($p < 0.05$), 0.665 + 0.047 ($p < 0.001$) and 0.684 + 0.048 ($p < 0.001$) respectively for amylase, lipase and ALP.

Discussion

Chronic kidney disease patients may have many liver and pancreatic diseases as comorbidities. Estimation of serum levels of enzymes like AST, ALT, ALP, GGT, amylase, and lipase still remains the main method for diagnosing these liver and pancreatic conditions like hepatitis, alcoholic cirrhosis, nonalcoholic steatohepatitis (NASH),



Graph 1: Comparison of all parameters in controls, CKD without ESRD and ESRD patients



Graph 2: Correlation of eGFR with ALP, amylase and lipase

Table 2: Correlation analysis of eGFR with liver and pancreatic enzymes in controls and CKD patients

	Controls (n = *100*)		*CKD patients* (n = *200*)	
	r value	*p-value*	*r value*	*p value*
eGFR and AST	−0.18	0.23	0.04	0.58
eGFR and ALT	−0.23	0.09	0.09	0.20
eGFR and ALP	0.046	0.76	−0.47	0.001
eGFR and GGT	−0.23	0.13	0.03	0.73
eGFR and amylase	−0.18	0.35	−0.29	0.001
eGFR and lipase	0.005	0.78	−0.40	0.001

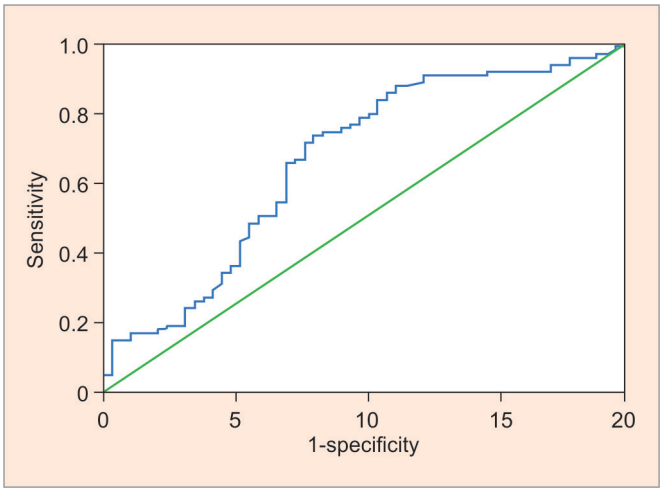
$p < 0.05$ is statistically significant

Table 3: Spearman's correlation analysis of eGFR with liver and pancreatic enzymes in 3 study groups

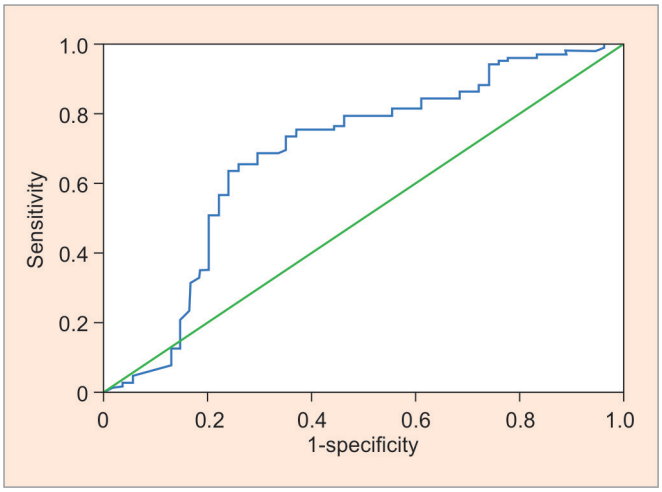
	Controls (n = *100*)		*CKD without ESRD* (n = *100*)		*ESRD* (n = *100*)	
	r value	*p-value*	*r value*	*p-value*	*r value*	*p value*
eGFR and AST	−0.18	0.23	−0.12	0.26	0.06	0.55
eGFR and ALT	−0.23	0.09	−0.02	0.87	0.18	0.09
eGFR and ALP	0.046	0.76	−0.54	0.001	−0.42	0.001
eGFR and GGT	−0.23	0.13	0.25	0.024	−0.06	0.06
eGFR and amylase	−0.18	0.35	−0.41	0.001	−0.65	0.001
eGFR and lipase	0.005	0.78	−0.42	0.001	−0.46	0.001

Table 4: Area under curve, sensitivity and specificity, cut-off levels of eGFR for amylase, lipase and ALP.

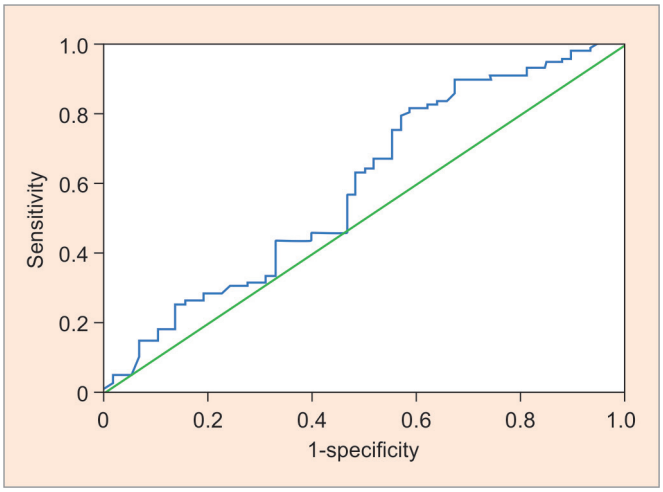
	Cut-off value of eGFR						
Parameters	*Cut off value of eGFR (ml/min)*	*Area under curve*	*SE*	*95% CI*	*p value*	*Sensitivity (%)*	*Specificity (%)*
Amylase	40	0.595	0.049	0.49- 0.69	<0.05	90	79
Lipase	48	0.665	0.047	0.57- 0.75	<0.001	94	86
ALP	47	0.684	0.048	0.59- 0.78	<0.001	96	80



Graph 3: ROC curve for cutoff point for eGFR for predicting lipase



Graph 4: ROC curve for cutoff point for eGFR for predicting ALP



Graph 5: ROC curve for cutoff point for eGFR for predicting amylase

pancreatitis, etc. Measurement of these enzyme levels not only help in diagnosis but also help in assessing the treatment, monitoring the disease process and assessing the severity of the disease. We compared these enzyme levels in controls, CKD without ESRD and CKD with ESRD to confirm whether the already existing reference ranges will hold good for assessing liver and pancreatic function in CKD patients.

The results of our study showed that the serum levels of AST and ALT (transaminases) were significantly low in CKD patients without ESRD as well as in ESRD patients as compared to controls; even though the mean values of transaminases in CKD without ESRD and ESRD groups were within the reference range only. There was a marked difference in these levels between CKD without ESRD and CKD with ESRD though not statistically significant. Serum ALP, GGT, amylase and lipase levels were significantly increased in CKD without ESRD and in CKD with ESRD patients as compared to controls. ALP, amylase, and lipase were raised in ESRD as compared to CKD with no ESRD. There was a strong negative correlation between estimated GFR and the serum ALP levels and pancreatic enzymes (amylase and lipase) in all CKD patients taken together as well as in both subgroups (CKD without ESRD and with ESRD).

Reduction in transaminase levels in CKD patients with and without ESRD was also observed in few studies [13-16] which are in support of our study results. Studies among hemodialysis patients also show a similar decrease in serum aminotransferases level.[17] In studies among patients infected with HCV, it was shown that HCV infected patients who also have CKD and are undergoing hemodialysis have lower serum levels of ALT than those with normal renal function.[18,19] Hence using the present reference ranges for serum aminotransferases in CKD patients both with and without ESRD, might result in missing a diagnosis of hepatic dysfunction in CKD. The use of standard reference values for aminotransferases to help detect liver disease is, therefore, less useful in patients undergoing chronic dialysis therapy. In one study of over 500 dialysis patients, standard cutoff values for aminotransferases were found to be poor indicators of active liver disease among hepatitis C antibody positive individuals who were undergoing liver biopsy.[18] We, therefore, recommend changing the upper limits of normal in ESRD (dialysis) patients

Mechanisms that are proposed for causing a decrease in transaminase levels in CKD to include a reduction in pyridoxal-5-phosphate which is a coenzyme of aminotransferases,[20] presence of ultraviolet absorbing materials and high levels of uremic toxins, decreased synthesis and inhibition of release of AST and ALT from hepatocytes or accelerated clearance from serum.[13,21] In contrast, another study reported that the mean serum vitamin B^6 and pyridoxal phosphate levels in dialysis patients were not significantly reduced as compared to controls. So, the authors concluded that

decreased serum AST and ALT levels in dialysis patients are not a result of vitamin B^6 deficiency.[22] A low serum aminotransferase level could also be due to water retention and hemodilution in patients of CKD.[13]

The elevated levels of ALP in CKD patients found in our study are in accordance with many other studies.[11,22] Proposed reasons for elevated levels of alkaline phosphatase is due to increased bone turnover in CKD. In CKD, vascular cells undergo osteoblastic differentiation and express several bone-associated proteins, which includes alkaline phosphatase also. The bone isoenzyme of ALP will be highly secreted in osteodystrophy, which is a complication of CKD. Osteodystrophy is a component of chronic kidney disease-mineral bone disorder (CKD-MBD). Several studies have proved increase levels of bone-specific ALP in advanced stages of CKD. In CKD, vascular cells undergo osteoblastic differentiation and express several bone-associated proteins, which includes alkaline phosphatase also.

Serum alkaline phosphatase activity can originate from liver, bone, intestine, or placenta; in most patients and normals, the majority of circulating activity consists of isoenzymes derived from either liver or bone. So total ALP level will not help in confirming the origin of ALP, i.e., from bone due to osteodystrophy or from liver due to liver damage. Hence determination of the tissue source of high ALP in CKD patients with suspected hepatobiliary dysfunction is difficult.

Gamma-glutamyl transferase (GGT) levels were also significantly elevated in both CKD patients with and without ESRD. This again adds to the difficulty in diagnosing or misdiagnosis of alcoholic and obstructive liver diseases in CKD patients.

Our study results showed a significant increase in pancreatic enzymes, amylase, and lipase in CKD patients with and without ESRD. ESRD patients had a significant increase in these levels as compared to CKD without ESRD. Our results are supported by various other studies.[23,24] Our study shows that as the severity of CKD increases (as is evidenced by a decrease in eGFR), there is an increase in amylase and lipase levels. Elevations in serum amylase among patients with renal failure or ESRD are most likely due to impaired renal clearance. In one study, the serum amylase began to rise only when the creatinine clearance dropped below 50 mL/minute.[25] The dialysis procedure alone does not appear to alter serum amylase. In one study, for example, no change was observed in serum amylase in samples obtained pre- and post-dialysis.[26] Amylase is one of the enzymes that is produced by the exocrine pancreas and a salivary gland that hydrolyzes starch is rapidly cleared by the kidney. Twenty percent of pancreatic enzymes are excreted by the kidney thus patients with end-stage renal disease have elevated levels of serum pancreatic enzymes. The serum amylase and lipase are elevated in patients with end-stage renal disease in absence of pancreatitis.[21,22] The highest levels of amylase and lipase are noted in advanced CKD patients, but marked elevations can also be seen in patients undergoing peritoneal dialysis .some studies have found that the cause of increased serum lipase in post-dialysis samples may be related to the use of heparin during dialysis. Heparin causes lipolytic activity, cross-reactivity with lipoprotein lipase and hepatic triglyceride lipase and ability to induce endothelial lipoprotein lipase.

There was a strong negative correlation for serum ALP, amylase and lipase with eGFR. In other words, as the severity of CKD increased, these enzyme levels also increased. This finding helps us in suggesting the need for setting new reference ranges for each stage of CKD or depending on the eGFR. The presently available reference range for hepatic and pancreatic enzymes will definitely lead to misdiagnosis or wrong diagnosis of hepatic and pancreatic dysfunction in CKD patients.

In the ROC curve analysis of our study, the cut off value of eGFR was found to be 40, 48 and 47 mL/minute for amylase lipase and ALP with a sensitivity of 90, 94 and 96% and specificity of 79, 86 and 80% respectively. That means a mean cut off of 50 mL/min can be kept for eGFR below which we should be cautious in diagnosing hepatic and pancreatic diseases in CKD. The results of this study helped us get a better and clear understanding about the use and significance of variations in the concentrations of levels of many liver and pancreatic enzymes in various stages of CKD. The present study was a hospital-based cross-sectional study with 300 subjects which are not enough to set reference range for hepatic and pancreatic enzymes in CKD. We would like to suggest the need of conducting such similar studies with very large sample size or population to set new reference ranges for hepatic and pancreatic enzymes in CKD patients ultimately preventing misdiagnosis and mismanagement of hepatic and pancreatic dysfunction in CKD. Diagnosis and monitoring of hepatitis, cirrhosis, and pancreatitis in different stages of CKD patients which remains a significant challenge in laboratory medicine can be made easy.

Conclusion

Our study concludes that serum transaminases level decrease in CKD patients and the levels are very low in ESRD patients. Serum ALP and pancreatic enzymes like amylase and lipase levels increase in CKD patients. The degree of increase of these enzymes is directly proportional to the severity of CKD. Hence our study results strongly suggest the invalidity of using the reference range of these hepatic and pancreatic enzymes in CKD patients and emphasize the need for new separate reference ranges for these enzymes in various stages of CKD which ultimately will help the treating physicians in diagnosis, monitoring and assessment of hepatic and pancreatic dysfunction in CKD patients. More studies have to be conducted with a larger number of the study population to establish new reference ranges for these enzymes in various stages of CKD. Studies should be conducted with CKD patients with coexisting hepatic and a pancreatic disease also is necessary.

Acknowledgments

The authors are thankful to Indian Council of Medical Research (ICMR) New Delhi for the funds given for this project entitled ''Serum liver and pancreatic enzymes in chronic kidney disease with and without end-stage renal disease: A comparative study'' [Reference ID: 2017-02847)].

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